REMARKS/ARGUMENTS

Claims 38, 40-41, 46, and 48 are under examination in this case. Claims 1-26, 34-37, and 44 had previously been canceled without prejudice. Claims 27-33 had previously been withdrawn. Claim 38 has been further amended for improved clarity and to better define the subject matter which Applicants regard as the invention. Claim 48 has been added as dependent claim to specifically claim the subject matter. Support is found throughout the Specification, particularly, from page 6, line 18 to page 7, line 12. Claims 39, 42-43, 45, and 47 have been canceled without prejudice in the present Amendment. However, Applicants reserve the right to file further divisional, continuation or continuation-in-part applications relating to the subject matter not encompassed by the amended claims. No new matter has been added with this Amendment.

Claim Rejection under 35 U.S.C. 112:

Claims 38-43 and 46-47 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants respectfully traverse this rejection.

Without acquiescing to this rejection and in the interest of advancing prosecution of this application, claim 38 has been amended to specify the method for preventing or treating malaria caused by a *Plasmodium* infection and that the agent used in the method is L-arginine, NO gas and/or an S-nitrosothiol compound.

Applicants submit that L-arginine is specifically disclosed as an agent which can be used to increase nitric oxide levels in a subject (see, *inter alia*, page 6, line 31 of the specification). Arginine is a known substrate of Nitric Oxide Synthase (NOS) as indicated on page 11, lines 13-14 in the specification. In addition, increased L-arginine concentrations are known to concomitantly increase NO levels in human subjects (for

example. see Lopansri *et al.* 2003 *Lancet* 361:676-678; Boger and Bode-Boger 2001 *Annu. Rev. Pharmacol. Toxicol.* 41:79-99, attached herewith as Exhibits A and B).

Lopansri *et al.* shows particular arginine concentrations which are associated with cerebral malaria, uncomplicated malaria, and subjects with no malaria. Specifically, it is shown that increased arginine concentrations are strongly associated with a decrease in the severity of malaria or the absence of malaria in a subject. These studies clearly confirm the claimed invention that certain levels of L-arginine can provide protective effects against malaria.

The Office Action alleges that the present specification does not describe the details of how to administer the compounds contemplated by the claims. Applicants submit that a person of ordinary skill in the art would be well aware as to how L-arginine can be administered. L-arginine has been administered to human subjects via the interarterial, intravenous and oral routes in the treatment of a range of diseases including, *inter alia*, cardiovascular diseases (Boger and Bode-Boger 2001 *supra*) and sickle cell disease (Morris *et al.* 2001 *Brit. J. Hematol.* 111:498-500, submitted herewith as Exhibit C). The present specification provides general guidelines from page 18, line 5 to page 21, line 4. Accordingly, Applicants submit that a person of ordinary skill in the art would be able to administer an effective amount of L-arginine to a human subject in order to enhance nitric oxide production to prevent or treat malaria depending on particular conditions of the subject (e.g. body weight, severity of the disease etc). Similarly, the use of NO gas to increase NO levels in a subject is also specifically disclosed in the present specification at, for example, page 4, line 1. Studies by Ng *et al.* (*Circulation Research* 2004 94:559-565) further confirm the claimed method. Specifically, it is disclosed that inhaled NO gas forms, *inter alia*, S-nitrosothiols which act as "transport molecules" for the NO. This paper also reports the concentrations of S-nitroso-albumin and nitrite, that can be achieved from inhaled NO gas. In view of the disclosure of Ng et al., it is submitted that the claimed invention as it relates to the administration of NO gas is sufficiently enabled by the present specification.

Applicants further submit that the present specification discloses S-nitrosothiol compounds as preferred NO donors (see page 6, lines 18-26). Furthermore, the anti-malarial activity of these compounds is also specifically exemplified in the specification. Applicants further assert that the administration of S-nitrosothiol compounds to increase nitric oxide levels *in vivo* in human subjects is well known in the art as evidenced by the abstracts by Lees *et al.* 1996 *Obster. Gynecol.* 88:14-19; Molloy *et al.* 1998 *Circulation* 98:1372-1375; Kuo *et al.* 2004 *Surgery* 135:437-446; Snyder *et al.* 2002 *Am. J. Respir. Crit. Care Med.* 165:922-926; and Rassaf *et al.* 2002 *Circ. Res.* 2002 91:470-477, all of which are submitted herewith as Exhibits D-H. Specifically, these abstracts all disclose the administration of S-nitrosothiol compounds such as S-nitrosoglutathione and S-nitrocysteine as NO donors in human subjects. Accordingly, the aspect of the claims directed to the administration of S-nitrosothiol compounds to increase nitric oxide levels and thereby treat or prevent malaria should be considered to be enabled based on the present specification.

Regarding the *Plasmodium* species contemplated in the claims, it is submitted that the amended claims are limited to infections by *Plasmodium* species which are causative agents of malaria. Examples of such pathogens include *P. falciparum, P. ovale, P. vivax,* and *P. malariae*. The life cycle and pathogenesis of these *Plasmodium* species are all similar. Furthermore, as stated at page 14, lines 16-23 and Examples 12 of the present specification, one of the effects of NO is to reduce or inhibit excessive cytokine production by white cells or other cell types implicated in the pathogenesis of disease (e.g. malaria) caused by *Plasmodium* species. Since this excessive cytokine production is associated with malaria caused by any malaria-causing *Plasmodium* species, the claimed methods are applicable to the treatment of malaria caused by any *Plasmodium* species. In support of this point, the abstract of Anstey *et al.* (*Am J of Tropical Medicine and Hygiene* 2002 67(2):abst. 515) is submitted herewith as Exhibit I. Specifically, this abstract discloses that *P. vivax*-associated malaria is associated with reduced NOS activity and increased TNF activity. Accordingly, Applicants argue that

the claimed methods are applicable to the treatment of malaria caused by *Plasmodium* species other than *P. falciparum* such as *P. vivax*.

The Office Action states on page 3 that "[T]his example merely shows an in vitro treatment on parasitised red blood cells, not an in vivo treatment on human subjects... . There is no causal-effect relationship, i.e., decrease the severity of malaria disease. The data merely provides observation of the treatment on parasitised red blood cells with the RSNO. The issue is that whether this in vitro model is an adequate model to reflect the effectiveness of an in vivo treatment on human ... ."

Applicants do not agree with the above allegation. MPEP 2164.02 specifically states that "[W]hen considering the factors relating to a determination of non-enabling, if all the other factors point toward enablement, then the absence of working examples will not by itself render the invention non-enabled. ... Lack of working examples or lack of evidence that the claimed invention works as described should never be the sole reason for rejecting the claimed invention on the grounds of lack of enablement. ..."

Regarding the issue of correlation between the *in vitro* and *in vivo* data, MPEP 2164.02 further states that "[T]he issue of "correlation" is related to the issue of the presence or absence of working examples... . An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" ... if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate ... the examiner must also give reasons for a conclusion of lack of correlation for an *in vivo* and *in vitro* animal model example. ... A rigorous or an invariable exact correlation is not required as stated in Cross v. Iizuka, 753 F.2d 1040, 1050 224 USPQ 739, 747 (Fed. Cir. 1985)" (emphasis added).

Applicants assert that the present case represents an example which meets the above criteria and thus the claimed invention is considered to be enabled based on the

data and the examples disclosed in the specification. As stated in the specification, the inhibition of cytoadherence reduces the likehood of infection or of severe infection by *Plasmodium* species. Human erythrocytes under normal physiological conditions do not bind to postcapillary endothelium. However, intraerythrocytic parasitization by malaria parasites (e.g. *Plasmodium falciparum*) is characterized by the adhesion of infected erythrocytes to endothelium in specific tissues and organs such as the brain precipitating cerebral malaria and other complicated forms of the disease. The data shown in Figs. 1 and 2 demonstrate that SNO-cysteine treatment reduces cytoadherence of parasitised red cells. SNO-cysteine is a NO donor. The examples illustrate that the NO levels are inversely correlated with malaria disease severity. General guidelines regarding dosage and mode of administration of a given agent are provided in the specification (see pages 17-21). Considering the foregoing and the knowledge that was available in the art as a whole, Applicants submit that the claimed invention is sufficiently described in the specification in such a way to enable a person of ordinary skill in the art to make and use the invention.

Claims 38-43 and 45-47 are rejected under 35 U.S.C. 112, second paragraph, as allegedly indefinite. Applicants respectfully traverse this rejection.

Without acquiescing to this rejection, claim 38 has been amended to recite a method of treating or preventing malaria caused by a *Plasmodium* species. Applicants submit that the meaning of the term, "a *Plasmodium* species" in amended claim 38 is clear as recited and in view of the description provided in the specification in that the present invention is directed to *Plasmodium* species that are causative agents of malaria. Claim 38 has been further amended for improved clarity by reciting "in the subject" after the term "nitric oxide levels". However, Applicants submit that the meaning of the term, nitric oxide levels, is self-evident, i.e., the administration of an agent such as L-arginine in the claimed method results in increased levels of nitric oxide, systemically and/or in certain organs/ tissues/cells in the subject who received such administration (see specification, page 3, lines 29-30).

In summary, based on the foregoing amendments and arguments, Applicants request withdrawal of the rejection under 35 U.S.C. 112.

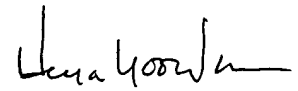
Concusion:

In view of the foregoing, it is submitted that this case is in condition for allowance, and passage to issuance is respectfully requested.

If there are further issues related to patentability, the courtesy of a telephone interview is requested, and the Examiner is invited to call to arrange a mutually convenient time.

This amendment is accompanied by a Petition for Extension of Time (3 months) and a check in the amount of $ 475 as required under 37 C.F.R. 1.17. It is believed that this amendment does not necessitate the payment of any additional fees under 37 C.F.R. 1.16-1.17. If the amount submitted is incorrect, however, please deduct from Deposit Account No. 07-1969 the appropriate fee for this submission and any extension of time required.

Respectfully submitted,



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